UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/610,935	07/06/2000	Brian W. Ward	SGM 6934.1	5148

321 7590 10/22/2003

SENNIGER POWERS LEAVITT AND ROEDEL
ONE METROPOLITAN SQUARE
16TH FLOOR
ST LOUIS, MO 63102

EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/610,935	WARD ET AL.	
	Examin r	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *11,13-16,20-22 and 42-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,13-16,20-22 and 42-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application (PTO-152)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .	6) ☐ Other: .

DETAILED ACTION

Supplemental Office Action

1. The following is a Supplemental Office Action. The period of response is reset from the mailing date of this Office action.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 11, 13-16, 20-22, and 42-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

4. For convenience, claims 11, 42, 48, and 54, the sole independent claims under consideration, are reproduced below.

11. (twice amended) A composition comprising a thermostable DNA polymerase for an *ex-vivo* polymerase reaction in which a nucleic acid polymer product complementary to a nucleic acid polymer template is prepared, and detectible anionic tracer dye compatible with the thermostable DNA polymerase, the composition being substantially free of the nucleic acid polymer template and having an optical density of about 5 to about 500 at a visible wavelength of maximal tracer absorbance.

42. A composition for an *ex-vivo* polymerase reaction in which a nucleic acid polymer product complementary to a nucleic acid polymer template is prepared, the composition comprising Taq DNA polymerase and an anionic tracer dye which visually has a red appearance and a peak visible absorbance wavelenth at between 430 and 617 nm, the composition being substantially free of the nucleic acid polymer template.

48. A composition for an *ex-vivo* polymerase reaction in which a nucleic acid polymer product complementary to a nucleic acid polymer template is prepared, the composition comprising Taq DNA polymerase and an anionic tracer dye consisting essentially of acid red 1 and acid violet 5, the tracer dye having an optical density of about 5 to about 500 at a visible wavelength of maximal tracer absorbance, the composition being substantially free of the nucleic acid polymer template.

54. A composition for an *ex-vivo* polymerase reaction in which a nucleic acid polymer product complementary to a nucleic acid polymer template is prepared, the composition comprising Taq DNA polymerase and an anionic tracer dye consisting of acid red 1 and acid violet 5, the tracer dye having an optical density of about 300 at a visible wavelength of maximal tracer absorbance, the composition being substantially free of the nucleic acid polymer template.

5. As presently worded, the composition of claims 11 and 42 must comprise a thermostable DNA polymerase and an anionic tracer dye, be substantially free of template and have an optical density from about 5 to about 500 (claim 11 and 48) or any optical density as is the case of claims 42 and 54. Table 1, found at pages 19-23, provides a listing of "Dyes initially considered", have maximal absorbance from 430 to 617. Page 25, first paragraph, states that of he listing of "dyes initially considered," only 20 were evaluated. Page 26, first paragraph, states that PCR toxicity was observed for some of the 20 dyes examined and were eliminated from the group of suitable dyes. Page 27, second paragraph, states that desalted dyes were less toxic as compared to crude dyes, and that ammonium salts of the dyes were the most toxic. As presently

worded, the claimed compositions encompass both crude dye preparations a well as ammonium salts thereof. The specification, however, does not reasonably suggest that applicant was in possession of compositions that comprise either crude preparations of dyes or ammonium salts thereof, regardless of their absorbance.

6. While the specification teaches that dyes that have a maximum absorbance from 450 to 570 were evaluated, the data shows that the only dye compositions actually found suitable were those that range between 508 and 532. Indeed, the record does not support the position that any dye composition was found suitable where the dye had an absorbance below that of 508 or above 532. While dyes within the range of 450 to 570 may have been eliminated because of aesthetic instead of technical reasons (too yellow/orange or too purple; page 25 of the disclosure), the record also clearly states that others were eliminated because they a) "lacked sufficient solubility," b) created a colored DNA pellet; and/or c) proved to be toxic to the polymerase. The specification dos not reasonably suggest how one of skill in the art would be able to recognize other dyes that would sufficiently soluble, not stain a DNA pellet, and not be toxic to the polymerase. As noted by applicant at page 27, lines 13-14, the dyes originally considered were "derived from unrelated applications." Accordingly, there is no common feature that would allow for the skilled artisan to recognize those dye members that fall within the claimed genus f compositions from those dyes that fall without.

7. A review of the specification fails to find such a composition being described in such full and concise terms as to reasonably suggest that applicant was in possession of such a composition at the time of filing.

8. In Table 1 applicant identifies over 180 red dyes that were evaluated. Table 2 lists 40 anionic dyes that were selected for further study. Upon review of Table 2, only four dyes, Acid Red 4, Acid Red 1, Amaranth, and Acid Violet 5 were found to be suitable. While the specification suggests that other colored dyes may be useful in the claimed composition, the specification has not been found to provide an adequate written description of these dyes.

9. A review of the specification fails to find where any composition has been formulated with any of these four dyes such that it would have "an optical density greater than about 5 at a visible wavelength of maximal tracer absorbance," would also have a density of "at least about 1.01 g/cm^3" or "at least about 1.1 g/cm^3" (claims 11-14). As presently worded, the optical density encompasses values ranging up to about 500. Clearly, the specification has not provided an adequate written description of such a composition. Additionally, claims 42-47 can have an optical density (absorbance) and density (gm/cm^3) of infinity. The record has not been found to provide an adequate written description of any such composition, regardless of dye component.

Response to arguments

10. At page 11 of the response applicant states:

It would therefore be clear to one of ordinary skill that, in spite of the fact that Applicants did not particularly demonstrate dyes of other colors in the Examples, Applicants were in possession of the claimed compositions wherein the dye is one other than the four specifically demonstrated in the examples. Indeed, one of skill would understand, especially in light of the specific teachings of the present specification as to how to obtain dyes compatible with a thermostable DNA polymerase, that the color of the dye does not affect the composition, and that Applicants purposeful demonstration of red anionic dyes only is a clear indication of their belief that any color tracer dye meeting the other claim limitations would suffice. Furthermore, one of skill would recognize that Applicants determination of the color of the dyes in their possession, and the decision to specifically test or not test dyes of a particular color as based solely on esthetics, indicates that Applicants were in possession of compositions that comprise these non-tested dyes.

11. The above argument ahs been fully considered and has not been found persuasive towards the withdrawal of the rejection. As noted above, the record clearly states that dyes were eliminated because they a) "lacked sufficient solubility," b) created a colored DNA pellet; and/or c) proved to be toxic to the polymerase. The specification does not reasonably suggest how one of skill in the art would be able to recognize other dyes that would sufficiently soluble, not stain a DNA pellet, and not be toxic to the polymerase. As noted by applicant at page 27, lines 13-14, the dyes originally considered were "derived from unrelated applications." Accordingly, there is no common feature that would allow for the skilled artisan to recognize those dye members that fall within the claimed genus f compositions from those dyes that fall without.

12. At page 9 of the response applicant states:

Furthermore, Applicants have demonstrated dyes of a red color that meet the limitations of the claimed invention. The demonstration of these particular red dyes meeting the limitations of the claims are sufficient to convey to one of skill in the art that Applicants were in possession of all such colored dyes that meet the same limitations.

Specifically, Applicants were in possession of dyes of other colors. Applicants screened numerous dyes based upon various factors, some of which were based upon performance characteristics, and others that were not. Of the factors that were not

While agreement is reached in that acid red 1 and acid violet 5 do meet the claim requirements, claims 11, 16-20, and 42-47, unlike claim 54, is not so limited. Agreement is reached in that applicant did screen a number of dyes, but that the vast majority has not been shown to meet the claim requirements when combined with the other requisite components of the composition. Table 1 only provides a partial listing of starting materials from which the claimed composition could be made from. As shown in the disclosure, dyes were eliminated on technical, a well as aesthetic reasons. In view of the innumerable technical reasons to consider, and the general unrelatedness of the dyes to one another, the disclosure does not provide an adequate written description of just which dyes would work in the composition. While one may argue that it would take undue experimentation to identify others, or that it would be obvious to those of skill in the art to determine which dyes are included, enablement and obviousness cannot be relied upon in satisfying the written description requirement. Attention is directed to the decision of *Vas-Cath Inc. v. Mahurkar* 19 USPQ2d 1111 (CAFC, 1991):

> This court in *Wilder* (and the CCPA before it) clearly recognized, and we hereby reaffirm, that 35 USC 112, first paragraph, requires a "written description of the invention" which is separate and distinct from the enablement requirement. The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the "applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Attention is also directed to the decision in *University of California v. Eli Lilly and Co.* (Fed. Cir. 1997) 43 USPQ2d at 1405, citing *Lockwood v. American Airlines Inc.* (Fed. Cir. 1997) 41 USPQ2d at 1966:

> Recently, we held that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention.

13. While applicant is not required to teach each and every possible combination in order to satisfy the requirements under 35 USC 12, first paragraph, the level of disclosure required must reasonably suggest that applicant was in possession of the full genus at the time of filing. Such full disclosure has not been found in the instant application. In support of this position, attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.
>
> ***
>
> We are of the opinion that a genus containing such a large number of species cannot properly be identified by the mere recitation or reduction to practice of four or five of them. As was pointed out by the examiner, four species might be held to support a genus, if such genus is disclosed in clear language; but where those species must be relied on not only to illustrate the genus but to define what it is, the situation is otherwise. (Emphasis added.)

14. In view of the breadth of scope of the claims, the limited disclosure in support thereof, and the recognized need to disclose a sufficiently representative number of examples, and the lack of convincing evidence to the contrary, claims 11, 13-16, 20-22, and 42-54 are rejected under 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 11, 13-16, 20-22 and 42-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Köster et al. (US Patent 5,928,906), in view of Nardone et al. (US Patent 6,117,986).

19. For purposes of examination the claimed composition has been interpreted as allowing for one or more of the component dyes to be associated with a nucleotide that could also be part of a nucleotide sequence, e.g., a labeled primer. While the claimed composition is defined as being "substantially free of the nucleic acid polymer template," such does not limit in any way the presence of non-template nucleic acid polymers, including that of primers. In support of this interpretation of the claim attention is directed to the following passage from page 16 of the disclosure:

> provided in ...
>
> Examples of essential reagents which can be combined with loading buffer components to formulate a composition of the present invention are: enzyme, concentrated enzyme buffer (e.g. 10X buffer), a nucleotide or primer reagent in the case of DNA or RNA polymerases, or a coenzyme such as NADPH or ATP. The preferred essential agent for this

20. While the claims are drafted in terms of how the composition is to be used, it is noted with particularity that the claims are drawn to a composition, not to a method of using same. Accordingly, the claims have been interpreted as encompassing any composition that meets the minimum requirements for components of the composition.

21. Köster et al., column 12, disclose a variety of compositions that comprise a tracer dye, and a thermostable DNA polymerase (Taq polymerase). It is noted with particularity that Köster et al., state that the template is added to this mixture.

1. The dyes described by Köster et al., are not defined in terms of their being anionic tracer dye, nor are they Acid red 1 or Acid Violet 5.

2. Nardone et al., column 3, disclose their unexpected discovery that dyes bound to mononucleotide precursors (applicant's nucleotide) can be incorporated into primers and that

these synthesized compounds can then be used in amplification reactions. Column 6 that Acid Red 1 and Acid Violet 5 were used to label or trace nucleic acids.

3. It would have been obvious to one of ordinary skill in the art at the time that the invention was made to have used anionic dyes such as Acid red 1 and Acid Violet 5 in the composition of Köster et al., as these anionic tracer dyes were known in the art to enhance nucleic acid assays. In view of the well-developed nature of the art, and the explicit guidance found therein, the ordinary artisan would have been highly motivated and would have had a most reasonable expectation of success.

Response to argument

4. At page 11, bridging to page 12 of the response argument is advanced that Köster et al., does not teach all of the claimed limitations.

5. Agreement is reached in that Köster et al., do not teach all of the limitations of the claimed invention. It is because of this aspect that the rejection was made over the combined teachings of Köster et al., and Nardone et al.

6. At page 12 of the response argument is advanced that the cited prior art cannot be combined. In particular:

> In combination, Köster et al. and Nardone et al. fail to render the claimed invention obvious. Köster et al. employ tracer dyes, but not one fitting the requirements of claim 11. In addition, Köster et al. disclose nothing of significance concerning their dyes. Nardone et al. disclose the use of acid red 1 and acid violet 5, but only as a *quencher* for a fluorescent dye. As such, what would have motivated a person of ordinary skill to substitute Nardone et al.'s quencher for Köster et al.'s dye? The Office provides no reason and none is apparent on this record. Rather, it appears the Office engaged in an impermissible hindsight reconstruction of th claimed invention. In the absence of a motivation to combine the references, a *prima facie* case of obviousness has not been established.[14]

7. This argument has been fully considered and has not been found persuasive. As stated above, the claims are drawn to a composition, not to a method of using the composition. While Nardone et al., may contemplate use of applicant's dye as a quencher, such does not negate the obviousness. As shown above, Köster et al., teach the use of tracer dyes and Nardone et al., unexpectedly find that dyes such as applicant acid red 1 and acid violet 5 can be incorporated into primers and primer extension products by use of Taq polymerase. The ordinary artisan, seeing the unexpected discovery of Nardone et al., would have been motivated to combine the labeled primers of Nardone et al., with the mixture of Köster et al. Additionally, the ordinary artisan, recognizing that dyes such as acid red 1 and acid violet 5 did not adversely affect the activity of a thermostable polymerase, e.g., Taq, would have been motivated to combine dyes such as acid red 1 and acid violet 5 in the mixture same mixture of Köster et al., as such could have been used either as a detectable label or as a quencher should additional labels be used, as suggested by Nardone et al. While applicant contemplates using the claimed composition in terms of a tracer, such intended use does not render he same composition non-obvious when the prior art reasonably suggests it combination, be it for the same or other purposes.

While the prior art has not been found to teach specific densities of the compositions, such formulations are considered to be the result of routine optimization. It is well settled that routine optimization is not patentable, even if it results in significant improvements over the prior art. In support of this position, attention is directed to the decision in *In re Aller, Lacey, and Hall*, 105 USPQ 233 (CCPA 1955):

> Normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. Under some circumstances, however, changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in

> degree from the results of the prior art. In re Dreyfus, 22 C.C.P.A. (Patents) 830, 73 F.2d 931, 24 USPQ 52; In re Waite et al., 35 C.C.P.A. (Patents) 1117, 168 F.2d 104, 77 USPQ 586. Such ranges are termed "critical" ranges, and the applicant has the burden of proving such criticality. In re Swenson et al., 30 C.C.P.A. (Patents) 809, 132 F.2d 1020, 56 USPQ 372; In re Scherl, 33 C.C.P.A. (Patents) 1193, 156 F.2d 72, 70 USPQ 204. However, even though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art. In re Sola, 22 C.C.P.A. (Patents) 1313, 77 F.2d 627, 25 USPQ 433; In re Normann et al., 32 C.C.P.A. (Patents) 1248, 150 F.2d 708, 66 USPQ 308; In re Irmscher, 32 C.C.P.A. (Patents) 1259, 150 F.2d 705, 66 USPQ 314. More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Swain et al., 33 C.C.P.A. (Patents) 1250, 156 F.2d 239, 70 USPQ 412; Minnesota Mining and Mfg. Co. v. Coe, 69 App. D.C. 217, 99 F.2d 986, 38 USPQ 213; Allen et al. v. Coe, 77 App. D. C. 324, 135 F.2d 11, 57 USPQ 136. (Emphasis added)

8. For the above reasons, and in the absence of convincing evidence to the contrary, the rejection is maintained.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

10. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

12. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

13. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
October 1, 2003